NEW DRUGS

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Lorlatinib

Approved indication: non-small cell lung cancer

Lorviqua (Pfizer)
25 mg and 100 mg tablets

The outcomes for patients with non-small cell lung cancer have improved with increased understanding of the genetics of the disease. Genetic rearrangements and mutations result in abnormal kinases. Examples include the c-ros oncogene (ROS1) and anaplastic lymphoma kinase (ALK). About 3–5% of non-small cell lung cancers are ALK-positive. These genetic discoveries led to tyrosine kinase inhibitors being used in treatment. Crizotinib was approved in 2014 for ALK-positive advanced non-small cell lung cancer. It was followed by so-called 'second-generation' drugs such as alectinib and ceritinib. Lorlatinib is a 'third-generation' drug that inhibits the ALK and ROS1 tyrosine kinases.

Lorlatinib can be given orally. It does not need to be swallowed with food but should be taken at the same time each day. The half-life is 24 hours with most of the dose being metabolised by cytochrome (CYP) P450 3A4 and UGT 1A4. Severe hepatotoxity can occur if lorlatinib is taken with strong inducers of CYP3A, such as rifampicin, so these drugs are contraindicated. The risk with moderate inducers is unknown so they should be avoided if possible. Strong inhibitors of CYP3A, such as itraconazole, should also be avoided. The effect of moderate–severe liver disease or severe kidney impairment on the concentrations of lorlatinib is unknown.

A range of doses was tested in an open-label trial. In phase I of the trial lorlatinib was given to 54 patients with locally advanced or metastatic non-small cell lung cancer. Brain metastases were present in 39 patients and 28 patients had already been treated with two or more tyrosine kinase inhibitors. Although tolerability was the main focus of the trial, 42% (11/26) of the previously treated patients with ALK-positive cancer responded to lorlatinib. A single daily dose of 100 mg was chosen for subsequent studies.[1]

In phase II of the trial, 275 patients with metastatic non-small cell lung cancer received lorlatinib. The 228 patients with ALK-positive cancer were divided into groups according to their previous treatment regimens, including 30 patients who had not been previously treated. There was also a group of 47 with ROS1-positive cancer. Across all the groups, 60% of the patients had brain metastases. In the untreated group 90% had an objective tumour response (complete or partial) to lorlatinib. For the 198 patients who had been treated with at least one tyrosine kinase inhibitor, 47% had an objective response. Intracranial responses were seen in 63% (51/81) previously treated patients with measurable lesions in the central nervous system. For all the patients with previously treated ALK-positive cancer, the median progression-free survival was 7.3 months.[2]

A separate analysis of the patients with ROS1-positive cancer reported an objective response to lorlatinib in 41% (28/69). An intracranial response was seen in 12 of the 24 patients with metastases who had been previously treated with crizotinib. Overall, the median progression-free survival was 8.5 months in previously treated patients.[3]

Adverse reactions are common and may require treatment to be reduced or stopped. In the phase II trial, 57% of the patients were able to continue taking lorlatinib for a median of 8.3 months.[2] The most frequent adverse effect is hyperlipidaemia and in many cases this has to be managed with lipid-lowering drugs. Oedema and peripheral neuropathy are also common. Less frequent but serious adverse reactions include interstitial lung disease and atrioventricular block. The most common reason for permanently stopping treatment in the phase II trial was cognitive effects.[2] Patients may also experience altered speech, hallucinations, mood changes and seizures.

As the clinical trials of lorlatinib are ongoing, lorlatinib has been granted a provisional approval in Australia. It is approved for patients with ALK-positive advanced non-small cell lung cancer that has progressed despite treatment. The approval specifies patients who have been treated with alectinib, ceritinib, or crizotinib and at least one other tyrosine kinase inhibitor. Lorlatinib is not approved for ROS1-positive cancer.

With several tyrosine kinase inhibitors now available, future research will need to determine what order to use them in. As 90% of previously untreated patients in the phase II trial had an objective response,[2] it is possible that lorlatinib may come to be used earlier in treatment. However, the response rate is a surrogate outcome and the effect of lorlatinib on overall survival is unknown.

T manufacturer provided the AusPAR and the product information

REFERENCES

1. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017;18:1590-9. https://doi.org/10.1016/s1470-2045(17)30680-0

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2. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19:1654-67. https://doi.org/10.1016/s1470-2045(18)30649-1
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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.